Complete Summary

GUIDELINE TITLE

Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. In: Sixth ACCP Consensus Conference on Antithrombotic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 2001 Jan;119(1 Suppl):220S-227S. [58 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Thromboembolism

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Pulmonary Medicine
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations for antithrombotic therapy in patients with prosthetic heart valves

TARGET POPULATION

1. Adults with mechanical heart valves, including:
    - St. Jude Medical bileaflet mechanical valves
    - Tilting disk valves
    - Various other types of valves
2. Adults with biological prosthetic heart valves

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention of Thromboembolism

1. Pharmacomanagement
    a. Oral anticoagulants
    b. Aspirin therapy
    c. Low doses of aspirin in combination with oral anticoagulants
    d. Heparin therapy
2. Establishment of target ranges for and monitoring of international normalized ratio

Note: Dipyridamole in combination with oral anticoagulants is considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Safety and efficacy of a given range of international normalized ratio
- Rates of thromboembolic events in target population treated with antithrombotic therapy
- Rates of major hemorrhage in target population treated with anticoagulant therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The participants reviewed information from an exhaustive review of the literature.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) (see "Rating Scheme for the Strength of the Recommendations") and the methodologic quality of the underlying evidence (A, B, C+, or C).

Grades of evidence for antithrombotic agents:

1A
Methodological strength of supporting evidence: randomized controlled trials without important limitations

1B
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)

1C+
Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies

1C
Methodological strength of supporting evidence: observation studies

2A
Methodological strength of supporting evidence: randomized controlled trials without important limitations

2B
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)

2C
Methodological strength of supporting evidence: observational studies

* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials with large loss to follow-up.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The strength of any recommendation depends on two factors: the trade-off between benefits and risks, and the strength of the methodology that leads to estimates of the treatment effect. The rating scheme used for this guideline captures these factors. The guideline developers grade the trade-off between benefits and risks in two categories: (1) the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and (2) the trade-off is less clear, and each patient's values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and risks and costs of therapy are small, treatment for average patients with compatible values and preferences can be confidently recommended.

If the balance between benefits and risks is uncertain, methodologically rigorous studies providing grade A evidence and recommendations may still be weak (grade 2). Uncertainty may come from less precise estimates of benefit, harm, or costs, or from small effect sizes.

There is an independent impact of validity/consistency and the balance of positive and negative impacts of treatment on the strength of recommendations. In situations when there is doubt about the value of the trade-off, any recommendation will be weaker, moving from grade 1 to grade 2.

Grade 1 recommendations can only be made when there are precise estimates of both benefit and harm, and the balance between the two clearly favors recommending or not recommending the intervention for the average patient with compatible values and preferences. Table 2 of the original guideline document summarizes how a number of factors can reduce the strength of a recommendation, moving it from grade 1 to grade 2. Uncertainty about a recommendation to treat may be introduced if the target event that is trying to be prevented is less important (confident recommendations are more likely to be made to prevent death or stroke than asymptomatic deep venous thrombosis); if the magnitude of risk reduction in the overall group is small; if the risk is low in a particular subgroup of patients; if the estimate of the treatment effect, reflected in a wide confidence interval (CI) around the effect, is imprecise; if there is substantial potential harm associated with therapy; or if there is an expectation for a wide divergence in values even among average or typical patients. Higher costs would also lead to weaker recommendations to treat.

The more balanced the trade-off between benefits and risks, the greater the influence of individual patient values in decision making. If they understand the benefits and risks, virtually all patients will take aspirin after myocardial infarction

or will comply with prophylaxis to reduce thromboembolism after hip replacement. Thus, one way of thinking about a grade 1 recommendation is that variability in patient values or individual physician values is unlikely to influence treatment choice in average or typical patients.

When the trade-off between benefits and risks is less clear, individual patient values will influence treatment decisions even among patients with average or typical preferences.

Grade 2 recommendations are those in which variation in patient values or individual physician values will often mandate different treatment choices, even among average or typical patients.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C) (see "Rating Scheme for the Strength of the Evidence").

Grades of recommendation for antithrombotic agents:

1A
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; can apply to most circumstances, without reservation

1B
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; likely to apply to most patients

1C+
Clarity of risk/benefit: risk/benefit clear
Implications: strong recommendation; can apply to most patients in most circumstances

1C
Clarity of risk/benefit: risk/benefit clear
Implications: intermediate-strength recommendation; may change when stronger evidence available

2A
Clarity of risk/benefit: risk/benefit unclear
Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B
Clarity of risk/benefit: risk/benefit unclear
Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

2C
Clarity of risk/benefit: risk/benefit unclear
Implications: very weak recommendation; other alternatives may be equally reasonable

COST ANALYSIS

While the American College of Chest Physicians conference participants considered cost in deciding on the strength of recommendations, the paucity of rigorous cost-effective analyses and the wide variability of costs across jurisdictions led the guideline developers to take a conservative approach to cost issues. That is, cost considerations influenced the recommendations and the grades of those recommendations only when the gradient between alternatives was very large.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial guidelines were prepared by the chapter committee (the primary authors) and then reviewed separately by the Committee Co-Chairs and methodology experts and finally by the entire group of Consensus Guideline participants.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

Excerpted by the National Guideline Clearinghouse (NGC):

The grading scheme is defined at the end of the Major Recommendations.

The following recommendations, in many instances, are made on the basis of sparse or incomplete data. As new data become available, the consensus recommendations may change. Treatment should always be based on appraisal of the individual patient, and it may properly differ from these consensus recommendations. The recommendations made by this committee differ somewhat from the recommendations of the European Society of Cardiology. In general, the guideline developers recommend lower levels of the international normalized ratio.

Mechanical Prosthetic Heart Valves

1. The guideline developers recommend that all patients with mechanical prosthetic heart valves receive oral anticoagulants (grade 1C+ recommendation).
2. The guideline developers recommend that unfractionated heparin or low molecular weight heparin be used until the international normalized ratio is at a therapeutic level for 2 consecutive days (grade 2C).
3. A target international normalized ratio of 2.5 (range, 2.0 to 3.0) is recommended for patients with a St. Jude Medical bileaflet valve (grade 1A), Carbomedics bileaflet valve (grade 1C+) or Medtronic-Hall tilting disk mechanical valve (grade 1C+) in the aortic position, provided the left atrium is of normal size and the patient is in sinus rhythm.
4. Levels of oral anticoagulants that prolong the international normalized ratio to a target of 3.0 (range, 2.5 to 3.5) are recommended for patients with tilting disk valves and bileaflet mechanical valves in the mitral position. (grade 1C+ recommendation).
5. Levels of oral anticoagulants that prolong the international normalized ratio to a target of 3.0 (range, 2.5 to 3.5) are recommended for patients with bileaflet mechanical aortic valves, who have atrial fibrillation (grade 1C+ recommendation, based on extrapolation of results in patients with atrial fibrillation who do not have prosthetic heart valves, and based on investigations in patients with mechanical heart valves who do not have atrial fibrillation).
6. An alternative recommendation for patients with tilting disk valves, bileaflet mechanical valves in the mitral position, or bileaflet mechanical valves in the aortic position plus atrial fibrillation is a target international normalized ratio of 2.5 (range, 2.0 to 3.0), in combination with aspirin 80 to 100 mg/day (grade 2C recommendation).
7. A target international normalized ratio of 3.0 (range, 2.5 to 3.5) in combination with aspirin 80 to 100 mg/day is recommended for patients with caged ball or caged disk valves (grade 2A recommendation, based on results of one randomized trial with various types of valves, one fourth of which were caged ball valves).
8. In patients who have mechanical valves and additional risk factors, the guideline developers recommend a target international normalized ratio of 3.0 (range, 2.5 to 3.5), combined with low doses of aspirin (80 to 100 mg/day) (grade 1C+ recommendation based on extrapolation of data from investigations, one of which used a different level of the international normalized ratio, and the patients may not have had additional risk factors).
9. In view of the advantageous effects of low-dose aspirin in combination with oral anticoagulants, the indications for dipyridamole require further evaluation.
10. For patients with mechanical prosthetic heart valves who suffer systemic embolism despite adequate therapy with oral anticoagulants, the guideline developers recommend aspirin 80 to 100 mg/day, in addition to oral anticoagulants, and maintenance of the international normalized ratio at target of 3.0 (range 2.5 to 3.5) (grade 1C+ recommendation based on extrapolation of data, in which aspirin 100 mg/day was used, sometimes with a higher international normalized ratio, in patients who did not have emboli).

Bioprosthetic Heart Valves

1. The guideline developers recommend that patients with bioprosthetic valves in the mitral position be treated for the first 3 months after valve insertion with oral anticoagulants (grade 1C+ recommendation). The guideline developers also recommend that patients with bioprosthetic valves in the aortic position be treated for the first 3 months after valve insertion with oral anticoagulants, but the evidence is less compelling (grade 2C recommendation).
2. In view of the high risk of thromboembolism during the first 3 months after valve replacement, heparin (low molecular weight or unfractionated) might be used until the international normalized ratio is at therapeutic levels for 2 consecutive days, but there is no evidence for this recommendation (grade 2C recommendation).
3. The guideline developers recommend a target international normalized ratio of 2.5 (range, 2.0 to 3.0) during the first 3 months after operation in patients with bioprosthetic valves in the mitral or aortic position (grade 1A recommendation based on an investigation that used an international normalized ratio of 2.0 to 2.3).
4. The guideline developers recommended that patients with bioprosthetic valves who have atrial fibrillation be treated with long-term oral anticoagulants, at a dose sufficient to prolong the international normalized ratio to 2.0 to 3.0 (goal 2.5). This 1C+ recommendation is based on randomized trials of patients with atrial fibrillation who did not have prosthetic heart valves (see article on atrial fibrillation). The need for anticoagulants is clear, based on these investigations. The dose of anticoagulants has not been established for patients with bioprosthetic valves and atrial fibrillation.
5. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, the consensus is to treat with long-term oral anticoagulants with a dose sufficient to prolong the international normalized ratio to a target of 2.5 (range, 2.0 to 3.0) (grade 1C). The duration is uncertain. This grade 1C recommendation is not based on published studies. Patients with bioprosthetic valves who have a permanent pacemaker are also at high risk for thromboemboli, but there is no evidence that oral anticoagulants are protective. The guideline developers suggest that anticoagulants (target international normalized ratio 2.5; range, 2.0 to 3.0) are optional in such patients (grade 2C recommendation).
6. It is recommended that patients with bioprosthetic valves who have a history of systemic embolism be treated with long-term oral anticoagulants. The international normalized ratio and duration are uncertain. The consensus is to treat with oral anticoagulants 3 to 12 months, at doses sufficient to prolong the target international normalized ratio to 2.5 (range, 2.5 to 3.0). This grade 2C recommendation is not based on published studies.
7. Among patients with bioprosthetic valves who are in sinus rhythm, the guideline developers recommend long-term therapy with aspirin 80 mg/day as protection against thromboembolism (grade 2C).

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodologic quality of the underlying evidence (A, B, C+, or C).

Definitions:

Grades of recommendations:

1A

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: randomized controlled trials without important limitations
Implications: strong recommendation; can apply to most circumstances, without reservation

1B

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)
Implications: strong recommendation; likely to apply to most patients

1C+

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: no randomized controlled trials, but randomized controlled trial results can be unequivocally extrapolated; or, overwhelming evidence from observational studies
Implications: strong recommendation; can apply to most patients in most circumstances

1C

Clarity of risk/benefit: risk/benefit clear
Methodological strength of supporting evidence: observation studies
Implications: intermediate-strength recommendation; may change when stronger evidence available

2A

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: randomized controlled trials without important limitations
Implications: intermediate strength recommendation; best action may differ, depending on circumstances or patients' societal values

2B

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: randomized controlled trials with important limitations (inconsistent results, methodologic flaws*)
Implications: weak recommendation; alternative approaches likely to be better for some patients under some circumstances

2C

Clarity of risk/benefit: risk/benefit unclear
Methodological strength of supporting evidence: observational studies

Implications: very weak recommendation; other alternatives may be equally reasonable

* Such situations include randomized controlled trials with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and randomized controlled trials with large loss to follow-up.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified for each recommendation (refer to "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of antithrombotic therapy and establishment of optimal international normalized ratio in patients with mechanical and biological prosthetic heart valves may prevent thromboembolic events, while reducing the risk of adverse effects of antithrombotic therapy, such as major bleeding.

POTENTIAL HARMS

The primary adverse affect of anticoagulants is bleeding. Data from several individual reports show varying frequencies of bleeding with increasing levels of the international normalized ratio (see Table 3 in the original guideline document).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Interpreting the Recommendations

The authors of these guidelines offer recommendations that should not be construed as dictates by the readers, including clinicians, third-party payers, institutional review committees, and courts. In general, anything other than a 1A recommendation indicates that the chapter authors acknowledge that other interpretations of the evidence and other clinical policies may be reasonable and appropriate. Even grade 1A recommendations will not apply to all circumstances and all patients. For instance, the guideline developers have been conservative in their considerations of cost, and have seldom downgraded recommendations from 1 to 2 on the basis of expense. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public

far more than some of the interventions that the developers designate grade 1A. This will likely be true for all less-industrialized countries. However, a weak recommendation (2C) that reduces resource consumption may be more strongly indicated in less-industrialized countries.

Similarly, following grade 1A recommendations will at times not serve the best interests of patients with atypical values or preferences. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (prevents participation in contact sports, for instance) or because of the need for monitoring. For such patients, clinicians may reasonably conclude that following some grade 1A recommendations for anticoagulation will be a mistake. The same may be true for patients with particular comorbidities (such as a recent gastrointestinal bleed or a balance disorder with repeated falls) or other special circumstances (such as very advanced age).

The guideline developers trust that these observations convey their acknowledgment that no guidelines or recommendations can take into account the often compelling idiosyncrasies of individual clinical circumstances. No clinician and no one charged with evaluating the actions of a clinician should attempt to apply their recommendations in a rote or blanket fashion.

Most of the published investigations lack data that would permit a firm conclusion about the optimal antithrombotic regimen for specific patients. Patients rarely were stratified according to additional risk factors associated with the type and location of prosthetic valves. Most results of antithrombotic prophylaxis are from nonrandomized case series without controls. The safety and efficacy of a given range of international normalized ratio are usually reported on the basis of an intention-to-treat analysis rather than on the basis of the intensity of anticoagulation actually achieved. In some important investigations, less than half of the international normalized ratios were in the target range. These limitations weaken the basis on which therapeutic recommendations can be made.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 2001 Jan;119(1 Suppl):220S-227S. [58 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Jan

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

Funding was supplied by DuPont Pharmaceuticals.

GUIDELINE COMMITTEE

American College of Chest Physicians Consensus Panel on Antithrombotic Therapy

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the Chest - The Cardiopulmonary and Critical Care Journal Web site.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Sixth ACCP Consensus Conference on Antithrombotic Therapy (2001): quick reference guide for clinicians. Northbrook, IL: ACCP, 2001.

Electronic copies: Available in from the American College of Chest Physicians Web site. (Downloadable files intended for use with Palm OS compatible devices are available.)

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348, or by calling 1 (800) 343-2227.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 30, 2001. The information was verified by the guideline developer on September 27, 2001.

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